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10/559,783	12/08/2005	Mitsuko Kosaka	64614(70904)	1080

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,783	KOSAKA, MITSUKO	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14 and 17-25* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-11 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 November 2007 has been entered.

Status of Claims

2. The amendment filed on 19 November 2007 has been entered into the record and have been fully considered. Claim 1 is amended. New claims 17-25 are added. Claims 15-16 are canceled.

3. Claims 1-6, 8-11 and 17-25, drawn to a method for producing tissue cells, that are myocardial cells, comprising culturing iris pigment epithelial cells and obtaining pluripotent cells therefrom, are being considered in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

4. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (19 November 2007).

5. Rejection of claims 1-6, 8-11 and 15 under 35 U.S.C. 112, first paragraph, written description is withdrawn, because of amendment of the claims.

Claim rejections maintained/new grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim fails to identify the metes and bounds of the related subject matter and how that could be ascertained in the stated invention.

7. Claims 20 and 22 are rejected, as being vague and unclear, and incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is not ascertainable as to how the culturing of iris cells in serum containing media can generate myocardial cells

without differentiation. The omitted steps are: the method steps for obtaining (differentiating) myocardial cells from iris cells.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 19-21, 23-25, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. The claims are drawn to a method for producing tissue cells comprising: (i) obtaining iris pigment epithelial cells and dissociating the isolated cells; (ii) culturing epithelial cells by floated coagulated mass in serum free media supplemented with N2 supplement and fibroblast growth factor-2 (FGF-2) (claim 19); (iii) test the cells for a gene specific for stem cells like Oct-3/4 (claims 24, 25); (iv) culturing the cells in serum containing media on a dish coated with extracellular matrix components, wherein the media contains a growth factor (e.g. FGF2, EGF, etc.) (claims 20, 21, 23). It is noted that although the claims do not explicitly recite "differentiation", claim 20 implicitly indicates the process of differentiation of stem cells expressing Oct-3/4 to form cells, e.g. myocardial cells

(see claim 22). Claims 20, 21, and 23, are thus broadly interpreted as culturing of cells in serum containing media, plus other growth factors, so as to induce differentiation to other cell types.

10. The specification of the instant application teaches that the iris pigment epithelial cells are obtained from the eyeball of a chick, followed by selective culturing of the cells using the (neurosphere) method of floated coagulated mass culture (Example1, pages 18-20). The specification further demonstrates the expression of Oct-3/4 gene in the iris tissue (Figures 6A and 6B), from 11 days and 3-month old rats (page 22, Example 3), as well as the expression of myocardial genes in the differentiated cells (Figure 4B). However, the brief description in the specification of one example of mesodermal cells (cardiac myocytes), one example of ectodermal cells (iris), does not provide adequate written description of an entire genus of stem cells that are differentiable and express Oct-3/4, after culturing of iris pigment epithelial cells. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of specific physiological characteristics, physical and/or chemical properties, functional features, structure/function correlation, or any combination thereof. However, in this case, the specification has not shown a relationship between the claimed genus of stem cells, derived from the iris pigment epithelial cells.

11. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

12. The skilled artisan cannot envision the entire genus of differentiable stem cells expressing Oct-3/4, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

13. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

14. Therefore, only methods of generation of cells of the myocardium, and iris, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-6, 8-11, 17 and 18, are rejected under 35 U.S.C. 103(a) as being

unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998), and Haruta et al., (Nat Neurosc 4: 1163-1164, 2001); in view of Reynolds and Weiss (Sc. 255: 1707-1710, 1992).

18. The claims are drawn to a method for producing myocardial tissue cells comprising: (i) obtaining iris pigment epithelial cells from an eyeball of a postnatal animal, for example, chicken, mouse, rat or human, by enzyme treatment (claims 1-3, 5-6); (ii) culturing epithelial cells by floated coagulated mass culturing technique to obtain pluripotent stem cells, that are Oct-3/4 positive, and/or tridermic differentiable (claim 1, 4). The claims further specify that the differentiation inducing conditions comprise culture of the cells in the presence of serum (fetal calf or avian) with a growth factor (FGF or EGF) (claims 8-11). Furthermore, the claims recite testing for the expression of one gene selected from GATA4, Nkx2.5, myosin etc. specific for myocardial cells (claims 17 and 18).

19. Kosaka et al. teach the removal of eyeballs from 1 day old (postnatal) chicken, thereafter isolating the pigmented epithelial cells from the iris into a single cell suspension after treatment with 0.1% trypsin in PBS (page 246, column 1, "Preparation of cell"). Kosaka et al. further teach the growth of the iris derived pigmented epithelial cells in culture for 18 days before reaching confluency. The depigmented iris pigment epithelial cells are harvested and cultured for transdifferentiation to lens tissue (page 246, column 1, "Procedure for cell culture").

20. Kosaka et al. do not teach culture conditions necessary for differentiation.

21. Haruta et al. teach the differentiation of iris-derived cells (from adult rats) to rod photoreceptor (page 1163, column 2, para 1), in response to *Crx* gene transfer. Haruta et al. further teach the differentiation inducing culture conditions comprising culturing in the presence of 1% fetal bovine serum with 10ng/ml FGF, as growth factor.

22. Kosaka et al. and Haruta et al. do not teach the culturing of iris pigment epithelium cells by a floated coagulated mass culturing technique.

23. Reynolds and Weiss teach a cell culture method suggestive of the floated coagulated mass culturing technique using neurospheres. The reference teaches the proliferation of cells from adult mouse striatum in a culture system wherein the cells undergo cell division and form clusters, which migrate across the substrate (page 1708, figures 1A-1C; legend to figure 1). The reference further teaches that after 6-8 divisions, the spheres (or clusters) of cells are lifted off the substrate and floated in suspension (page 1708, figure 1D).

24. Kosaka et al., Haruta et al., and Reynolds and Weiss, do not explicitly teach the expression of Oct3/4. However, this limitation will be an inherent feature, since the combined references teach the same culture limitations of the instant application. Additionally, since the cells of Kosaka et al. and Haruta et al are derived from the same source as the instant application, are cultured under similar differentiation conditions, the three inherently display the same differentiation properties, and express similar marker, absent evidence to the

contrary. That the references are silent on the expression of the cardiac marker genes does not provide proof of the cell being different, particularly if the other conditions (as stated above) are satisfied.

25. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of culturing the iris pigment epithelial cells of Kosaka et al. and Haruta et al., to the floated coagulated mass culture technique as taught by Reynolds and Weiss. The person of ordinary skill in the art would have been motivated to use this technique for cell culture and differentiation as this would facilitate the selection of a specific cell type aggregate by antibody immuno-staining (Reynolds and Weiss, page 708, Figure 1E and 1F). The person of ordinary skill in the art would have expected success because the method of floated coagulated mass technique (or neurosphere), was well established and accepted in the art at the time the invention was made.

26. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's Response

27. Applicant traverses with the rejection because, while Kosaka and Haruta do not suggest or disclose a floated coagulated mass culturing technique for iris pigment epithelium cells, Reynolds teaches the coagulated mass culturing method only for neuronal cells. Applicant alleges that because it is difficult to

culture primary cells, and because the floated mass culturing technique was selectively useful for neuronal cells at the time of the filing of the instant invention, it would not be obvious to use a specific and specialized method of neuronal cells for a totally different cell, an epithelial cell. Therefore, Applicant asserts that the three references in combination would not provide a suggestion or motivation to a skilled worker, rather teach against the instant invention. Furthermore, Applicant continues that for reasons explained above, the iris pigment epithelium would allegedly not be expected to generate myocardial cells, or test for genes specific for such cells. Applicant concludes by asserting a "surprising element of the invention" that involves the ability to selectively culture iris pigment epithelial cells by the floated mass coagulation method to produce stem cells that can differentiate to various types of tissues.

28. Applicant's arguments have been fully considered but have not been found to be persuasive. A *prima facie* case of obviousness was correctly established, because Kosaka et al. and Haruta et al. teach culturing and differentiation of iris pigment epithelial cells, and Reynolds et al teach the floated coagulated mass culture method. The Office emphasizes that although Reynolds et al. teach the differentiation of the neurosphere to neural and neuroepithelial stem cells, the reference essentially teaches a technique for selective culturing and differentiation to various cell types, which can be broadly applied to various cells and tissues. This is further evidenced by the publication of Rezai et al., which demonstrates the isolation and culture of iris pigment epithelium cells,

wherein spherically shaped cellular structures are generated, thereafter aspirated and subcultured in separate dishes (Invest Opthalmol Vis Sci 38:2255-2260, 1997; Materials and Methods, page 2256, Isolation and Culture). Rezai et al. further state that the spheroid model is advantageous because of its high capacity of proliferation, resistance to differentiation for long periods and ability for transfers between culture dishes and form monolayers (page 2255, para 1). Additionally, the use of the neurosphere technique for selective culturing of the IPE cells was inherent in the instant specification (page 19, para 2).

29. Applicant further argues that Reynolds et al. do not teach IPE cell types and thus the neurosphere method cannot be a motivation for using for IPE cells. However, as stated in the previous Office Action, it is reiterated that neural, neuroepithelial and IPE cells are all ectodermal cells, and absent evidence to the contrary, the technique of using neurospheres for IPE cell differentiation in culture, would be obvious to one skilled in the art in view of Reynolds et al. Furthermore, in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom (*In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968)). Also, a reference must be considered, under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments, must be considered in determining obviousness (*In re Burckel* 201 USPQ 67 (CCPA 1979)).

30. Furthermore, although the references (Kosaka et al and Haruta et al) do not explicitly teach the differentiation to myocardial cells, this limitation will be an inherent feature, since the combined references teach the culture limitations of the instant claims. Additionally, since the cells of Kosaka et al. and Haruta et al are derived from the same source as the instant application, the three inherently display the same differentiation properties and express similar markers, absent evidence to the contrary. That the references are silent on the expression of the cardiac marker genes does not provide proof of the cell being different, particularly if the other conditions (as stated above) are satisfied.

31. For reasons stated in the Office Action dated 13 March 2007 (page 13, para 36), and reiterated herein, the claimed invention is *prima facie* obvious over the combined teachings of Kosaka et al., Haruta et al. and Reynolds and Weiss. Thus the rejection is maintained.

32. Claims 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998), and Haruta et al., (Nat Neurosc 4: 1163-1164, 2001); in view of Reynolds and Weiss (Sc. 255: 1707-1710, 1992).

33. The claims are drawn to a method for culturing iris pigment epithelial cells (i) as a floated coagulated mass in serum free media plus N2 supplement in combination with fibroblast growth factor-2 (FGF2), (ii) testing the cells for a gene or Oct-3/4 specific for stem cells, (iii) culturing the cells in serum

containing media, containing one growth factor such as FGF2, EGF, etc., wherein the culturing of cells is conducted in a dish coated with extracellular matrix components, and (iv) testing the cells for a gene specific for myocardial cells.

34. The teachings of Kosaka et al., Haruta et al., and Reynolds et al. are set forth above.

35. Kosaka et al. further teach the culture of chick iris pigment epithelial cells in medium supplemented with bFGF, in collagen coated dishes (page 246, col 1, para 1-3, Materials and Methods).

36. Additionally, Reynolds et al. teach the floated coagulated mass culturing technique in serum free media, comprising a defined hormone and salt mixture (comprising insulin, transferrin, progesterone, putrescine and selenium salt) (see Reynolds et al. page 1707, col 3, line 3; page 1709, Reference No. 7; also see cross reference No. 18 - Weiss et al. PNAS 83: 2238-2242, 1986; page 2238, Materials and Methods, para 1).

37. Neither Kosaka et al./Haruta et nor Reynolds et al. teach a process for culturing iris pigment epithelial cells in serum free media containing both N2 supplement and FGF. However, in the absence of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of the references and to use both N2 supplement and FGF (or FGF2). Each of these ingredients had been taught by the prior art to culture iris pigment epithelial cells and to be useful promoters for growth, maturation and

differentiation (Weiss et al., page 2242. conclulding para; Kosaka et al. page 248, col 1-2; figure 4, 5A, 5B). The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven* (205 USPQ 1069 (CCPA 1980)) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of culturing iris pigment epithelial cells in serum free media comprising N2 supplement and FGF2 individually as culture media supplements for the induction of growth and differentiation of cells, it would have been obvious to culture the iris pigment cells with both N2 supplement and FGF2, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as culture medium supplements for the same purpose of growth and differentiation of the iris pigment epithelial cells. One of ordinary skill in the art would have reasonably expected to isolate, culture and grow iris pigment cells with either or both of N2 supplement or FGF2, since both had been demonstrated in the prior art to be involved in the growth, maturation and differentiation of the iris pigment epithelial cells.

38. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

39. No claim is allowed

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

41. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

42. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
16 January 2008

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER